

VI. Biological and Biomedical Factors

A syphilis epidemic is not caused by a single isolated factor. Biological factors and biomedical factors contribute to the spread of syphilis. In this section, we will examine these factors based on a literature review.

A. Methods

An extensive literature search was conducted to identify relevant information regarding syphilis. The key words “syphilis”, “sex”, “drug”, “syphilis epidemic”, and “syphilis biology” were used for searching MEDLINE, a comprehensive medical literature database. A snowball approach was also used to obtain additional literature through references of MEDLINE-search identified articles. Available documents from local agencies and major STD and infectious disease textbooks were also reviewed. Findings are summarized below.

B. Findings

1. Biologic Factors

Syphilis is caused by *Treponema pallidum*, identified in 1905 by Schaudinn and Hoffman. It is an obligate human parasite. Nearly all cases of syphilis are acquired by direct sexual contact with lesions of an individual who has primary or secondary syphilis. Therefore; syphilis, excluding congenital syphilis, is a behavior-linked disease that results from unprotected sex (1, 2, 8). Several biological factors contribute to its rapid spread.

a. High transmission rate and low infectious dose

The transmission rate for syphilis is relatively high, especially after repeated exposures. The majority of syphilis is transmitted during the early stage of the disease because a patient is most infectious at this stage, especially when lesions are present. Among couples with frequent sexual contact, four out of five partners exposed to the infectious lesions of early syphilis will be infected. Much less transmission occurs when the index case has been infected for more than 4 years (22).

Epidemiological studies have shown that syphilis develops in about one third of exposed persons. In other words, without preventive measures, three of ten sexual encounters between an infected and an uninfected person will result in the transmission of syphilis. Empirical data from national syphilis control programs suggest that an untreated syphilis patient would generate 1.15 new infections during the 11-week period of P & S syphilis (5 weeks of primary syphilis and 6 weeks of secondary syphilis). At this level, in the absence of intervention, syphilis will propagate in the population (22). The exact number of bacterium needed to infect is unknown, but experimental intracutaneous injection of the agent required only 57 organisms (47). A high transmission rate and low infectious dose, coupled with multiple sexual partners, make it possible for a small group of infected patients to cause a syphilis epidemic.

b. Asymptomatic²² nature

The asymptomatic nature of syphilis is characterized by atypical lesions and painless lesions often in hidden areas. In 60-85% of patients, the infection is asymptomatic (5). In other words, 60-85% of infected patients either do not notice manifestations of disease or do not recognize them as a cause for concern. Atypical lesions or the absence of a primary skin lesion are common (1). The variations in clinical presentation depend on the number of organisms inoculated, the immune status of the patient, intercurrent antibiotic therapy, and whether the lesion becomes secondarily infected. The external genitalia are the frequently involved site. However, infections of the cervix, mouth, perianal area, and anal canal are also common (1). Because of the asymptomatic nature of the disease, signs and symptoms often do not alert infected patients sufficiently to seek diagnosis and treatment, therefore, providing more time and opportunities for syphilis to be transmitted to another person (45). In addition, P & S syphilis lesions will heal spontaneously within 2-8 weeks, creating a mistaken impression that it was not a serious problem (22).

c. Wide range of incubation period

The time interval between initial contact with an infectious agent and the onset of the primary stage (primary will occur but may not be recognized) varies widely, from 10 days to 90 days (2, 5). Animal experiments demonstrated an inverse relationship between numbers of treponemes inoculated and time required for development of the primary cutaneous lesion (26). This inverse relationship and the nature of slow growth of treponemes in humans probably accounts in part for the variability of the incubation period (26). This biological factor, combined with asymptomatic nature discussed above, makes contact tracing of certain high-risk groups (drug dealers and prostitutes, for example) very difficult. Consequently, the difference of contact-tracing of certain high-risk groups gives the opportunity for the disease to spread without much control.

d. Long period between infection and complications

If syphilis remains untreated, up to one-third of patients will develop neurosyphilis and cardiovascular syphilis in 2 to 50 years (2, 5). The long period of time from the initial infection to the development of serious complications reduces individual's perceived significance of syphilis and motivation to undertake preventive actions, which may contribute to the repeated syphilis infections among high-risk groups within the community.

e. Gender and age differences

Gender and age may influence the risk of acquiring or transmitting syphilis. The risk estimates for syphilis in women are much higher, given the same risk factors as their

²² Symptoms are those reported by the patient and signs are clinical findings; therefore, a patient could have a lesion, not recognize it to be anything of concern, and as a result not seek care. By definition this person would be asymptomatic even though an examination would find a lesion.

male counterparts. For example, 30% of all women exposed to syphilis during a single sexual encounter become infected while only 20% of men become infected (48). Many STDs are transmitted more easily from men to women than from women to men. This is because women are biologically more likely to become infected than men if exposed to a sexually transmitted pathogen (8). The primary stage of syphilis is often silent in women since the painless lesion is most often found on the cervix and is therefore not readily visible like a lesion found on a man's penis. Because primary syphilis is more likely to remain undetected in women, it results in delayed diagnosis and treatment, offering more opportunities for syphilis transmission (49).

2. Biomedical Factors

It was once an adage of medicine that "he who knew syphilis knew medicine." Before the introduction of penicillin, syphilis therapy required a 70-week course on an outpatient basis or a 5-10-day course in so-called "Rapid Treatment Centers" (1, 22). Penicillin therapy changed all that. In 1953, Benzathine Penicillin G, a repository form of penicillin, was developed, making possible the effective one-shot treatment of syphilis. Since that time, 2.4 million units of this preparation has been the recommended treatment for early syphilis (46, 50).

Syphilis holds a special place in the history of medicine as the "great imitator" for its being a complex systemic illness with protean clinical manifestations²³. Several biomedical factors suggest that early recognition and adequate treatment of syphilis patients and their sex partners are the essential means of preventing its propagation in the community. These factors are: 1) *T. pallidum*'s long division time (extended incubation period) provides prolonged opportunity to abort "incubating disease" because during the incubation stage the serologic tests for syphilis are negative, there are no signs or symptoms, and the person is not infectious; 2) *T. pallidum* remains exquisitely sensitive to long-acting benzathine penicillin; 3) treatment of syphilis is much easier than diagnosis (1,2,22, 26).

Early recognition of syphilis involves syphilis screening and clinical diagnosis. Syphilis screening tests are available. Syphilis seroepidemiological tools are inexpensive and tests are relatively simple to perform, highly sensitive and specific, and readily available (50). Literature suggests that targeted screening is more practical than mass screening. Positive screening tests are generally followed by a variety of confirmatory tests to substantiate the diagnosis.

²³ Syphilis is a systemic disease with a large variety of clinical presentations. For example, a genital ulcer in primary syphilis must be distinguished from ulcers in genital herpes, granuloma inguinale, drug eruptions, carcinoma, superficial fungal infections, traumatic lesions, and lichen planus. Patients in the secondary stage may complain of malaise, fever, headache, sore throat, and other systemic symptoms. Differential diagnosis of secondary syphilis includes a large number of diseases such as pityriasis rosea, drug eruptions, acute febrile exanthems, psoriasis, lichen planus, scabies, oral candidiasis, infectious mononucleosis, and infectious hepatitis. In addition, syphilis staging is imprecise and often arbitrary. There is a considerable overlap in the clinical manifestations of different stages, particularly with respect to neurologic and ophthalmologic complications (1, 26).

The clinical diagnosis of syphilis, difficult but crucial for both case finding and prevention, is based on its symptoms and signs. However, clinical diagnosis is an effective tool for syphilis control, which has produced the majority of such cases reported to public health authorities for at least half a century (41, 50).

The laboratory diagnosis of syphilis is based on visualization of *T. pallidum* and/or demonstration of antibodies either to this pathogen or to cardiolipin antigen. No single finding or test is in itself absolutely diagnostic of syphilis if we consider the possible human errors on testing. The most accurate single diagnostic factor is usually the darkfield or direct fluorescent antibody demonstration of *T. pallidum*. The accuracy of these two tests, however, depends on how and where the clinical specimen was obtained, how it was transported to the laboratory, and who performed the test (5, 22).

Early treatment of syphilis based on clinical diagnosis is inexpensive, simple, safe, and effective. The efficacy of penicillin for syphilis treatment is well established (50). There is no evidence that the efficacy of penicillin treatment of syphilis has diminished over 50 years (1, 44). Unlike many other bacteria, *T. pallidum* has not developed resistance to penicillin despite it being the syphilis treatment-of-choice for a half-century (22, 41, 50).

Although the efficacy of penicillin in the treatment of syphilis is well known, there has never been a well-controlled, carefully planned prospective study to determine the optimal dose or duration of therapy. There is evidence that *T. pallidum* can accept resistant plasmids, and the possibility exists that penicillin treatment may become inadequate in the future (1). Therefore, if we do not act in a timely manner, we could lose the window of opportunity for syphilis control.

C. Discussion

As summarized above, syphilis' unique biological factors favor the disease transmission in certain social environments (the "right" social-sex network with a core transmitter, for example) and certain population sub-groups, such as persons who engaged in high risk sexual behavior. Therefore, identifying syphilis favored social environments and specific sub-population groups of high risk will improve our effectiveness and efficiency of syphilis prevention and control.

From a biomedical point of view, syphilis is much easier to treat than to diagnose. Therefore, early recognition of syphilis (syphilis screening and clinical diagnosis) holds a key to control the spreading of syphilis in a community. Considering syphilis' biological factors, syphilis screening that focused on specific sub-population groups will produce a much better result.

The first fourteen months of Nashville's Jail Syphilis Screening Project (November 1999 to December 2000) detected 38.2% reported syphilis cases during that period. This suggested that if we fully understood and acted on the implications of

syphilis biomedical factors, we could not miss valuable prevention and control opportunities presented to us during a pre-epidemic period.

Clinical diagnosis is difficult but crucial in syphilis epidemic control. Considering the asymptomatic nature of the disease, it is likely that a significant proportion of primary and secondary syphilis cases would not seek specialized STD care. These cases could be diagnosed by health care providers not working at specialized STD clinics if the case presented to them and they were adequately trained in the diagnosis of syphilis. Anecdotal data suggests that some health care providers may not have adequate knowledge and/or equipment in making an accurate clinical diagnosis of syphilis. Some providers use “primary” to designate the patients’ first infection with syphilis rather than the initial stage of disease. This may suggest another missed opportunity in syphilis prevention and control. Therefore, it is important that all health care providers who may encounter potential syphilis cases should be offered the opportunity to develop competence in the clinical diagnosis of syphilis. From a biomedical factor point of view, such training of health care providers is essential to the syphilis elimination effort.

VII. Conclusions and Recommendations

Nashville has experienced a syphilis epidemic since 1996. The potential health and economic burdens are tremendous. This MHD epidemiological investigation examined the possible risk factors that may contribute to this epidemic.

Illegal sex and drug related activities are important contributors to Nashville's current syphilis epidemic. During the epidemic period, more syphilis cases engaged in sex and drug related criminal activities (number of cases with sex and drug related charges increased 87% and 122% , respectively). Furthermore, for these cases, there were more sex and drug related criminal activities or charges/arrests (the cases' sex and drug related charges increased 57% and 261%, respectively).

The highest percentage of sex and drug related criminal activities (6.4% and 18% respectively) was found in the 30-39 age group. The 30-39 age group also had the highest incidence in the epidemic. These findings suggest that illegal sex and/or drug activities in the 30-39 age group may contribute to the epidemic.

Criminal charges of illegal sex related activities among syphilis cases are 20% to 60% higher than comparison groups (syphilis-gonorrhea group: OR 1.17, 95% CI 1.06, 1.29; syphilis-chlamydia group: OR 1.46, 95% CI 1.19, 1.79; syphilis-non-STD group: OR 1.63, 95% CI 1.31, 2.02). For each additional sex related charge, the risk of syphilis acquisition increased 16.7% to 62.6%.

Syphilis cases in the homeless population may contribute to Nashville's current syphilis epidemic. A high syphilis incidence rate (419.9 cases per 100,000 female population during 1995-1998) among the sampled female homeless population suggests that the syphilis cases in the homeless population in Nashville may act as one of the important sources of the core groups in the community to spread syphilis. However, it is realized that this statement is based on limited data and further investigation is needed.

Underreporting/miscoding/misdiagnosis may be a potentially significant contributor to Nashville's current syphilis epidemic. Potentially unreported syphilis cases may contribute to Nashville's existing syphilis "core transmitters" pool. TennCare utilization data matching found that 312 TennCare provider-diagnosed P & S syphilis patients were not matched with MHD reported P & S syphilis cases during 1994-1998. Although the MHD STD Clinic audit data provided some evidence of underreporting and/or miscoding and/or misdiagnosis, the impact of underreporting and/or miscoding and/or misdiagnosis on Nashville's syphilis epidemic remains unknown. A study is warranted to investigate this issue.

An over-burdened public health system may have lost some opportunities to prevent Nashville's current syphilis epidemic. Missed opportunities for syphilis prevention and control may stem from two changes: 1) the decrease in public health services utilization (number of patients decreased 15.8%, the number of visits

decreased 6.3%, number of services decreased 4.5% from the pre-epidemic period to the epidemic period) likely due to the decrease in the MHD budget (decreased by 8.5% during 1995-1999); and 2) the possible increase of needs and demands for STD services in the community reflected by an increase in visits per patient and a decrease in the number of services per visit from the pre-epidemic period to the epidemic period.

The introduction of TennCare changed the utilization pattern of access to syphilis care in this community. This may act in two opposing ways. Many individuals (36% of the TennCare population) who were previously considered uninsured or uninsurable now have coverage. This should act to improve access to care. However, those patients who were covered under the traditional Medicaid program (64% of TennCare population) may now have fewer choices for primary care physicians. If the patient is not pleased with the care received within the network, some conditions such as an STD may remain untreated and ultimately contribute to the syphilis epidemic.

Nashville's environmental and ecological conditions provide soil for the current syphilis epidemic to grow. The analysis of population factors suggests that Nashville has a population basis for syphilis spread. The dynamics of the population (the high percentage of poverty in the population, the increasing trend in crime, a relatively higher percentage of females in the population, fast growth of the Nashville Metropolitan Area) provide a favorable social environment for syphilis transmission. Risky sexual behaviors (early initiation of sexual activities, early sexual experiences, multiple sexual partners, failure to use condoms, alcohol and drug involvement in sex) among a significant proportion of Nashville's youth and adults (18.8% - 54.4% of selected youth groups surveyed engaged in risky sexual behaviors, 14.6%-41.7% of selected adults surveyed engaged in different risky sex behaviors), the existence of syphilis core groups in the community, and missed diagnosis and treatment opportunities for a large number of primary syphilis cases, combined to offer the necessary conditions for the occurrence of the syphilis epidemic.

The conjunction of syphilis's unique biological and biomedical features with a favorable social environment results in Nashville's current syphilis epidemic. Syphilis's unique biological and biomedical features are characterized by a high transmission rate and low infectious dose, its asymptomatic nature, a wide range of incubation, a long period between infection and complications, gender and race differences in acquisition, and difficulties in clinical diagnosis. If a desired environment that includes all necessary factors exists, as is the case in Nashville, the occurrence of a syphilis epidemic should not be surprising.

As documented in this report, it is clear that syphilis should be considered a social disease. Although the transmission of syphilis between and among sexually active persons is a direct result of individual behaviors, the social factors discussed above generate and support the environmental and ecological conditions that increase and intensify the risk of each individual's behavior and thereby serve to promote and sustain the epidemic (51). Therefore, it is vital to address these social factors in order

to control the syphilis epidemic. This requires more collaborative and comprehensive public health approaches to achieve the control of the epidemic and the elimination of syphilis in our community. CDC's five syphilis elimination strategies should be used to guide our actions. Specifically, it is recommended that we:

1. **Continue to enhance our syphilis surveillance system.** The surveillance system is the foundation for preventing and controlling syphilis in Nashville. Nashville's system needs to be enhanced.

The fact that illegal sex and drug related activities are associated with the acquisition of syphilis reconfirmed the rationale of Nashville's jail syphilis screening project. As an active component of MHD's syphilis surveillance system, the Davidson County Criminal Justice Center Syphilis Jail Screening Project was deployed in November 1999. A preliminary analysis of the first fourteen months data found that syphilis cases detected by the jail screening project accounted for 38.2% of reported cases. This timely, sensitive, and targeted syphilis surveillance should prove to be one of the most effective tools in controlling syphilis in our community.

Identification of defects in our current syphilis surveillance system presents a new opportunity for us to enhance Nashville's county-wide syphilis surveillance system. TennCare utilization data may be used as an important new source for active syphilis surveillance. It is also recommended that a further investigation be conducted to answer the questions in the "underreporting and/or misdiagnosis" sub-section of this report on page 51.

2. **Continue to strengthen community involvement and partnership.** The syphilis epidemic is a public health issue. Public health issues are best dealt with when the community is mobilized. MHD Community Health Action Team's STD Free effort demonstrated effectiveness of mobilizing the community by promoting awareness of the syphilis epidemic and educating high risk groups regarding healthy sexual behaviors. It is recommended that the STD Free initiative be continued and enhanced to maintain a strong community partnership to fight syphilis.
3. **Expand our outbreak response effort to include the homeless population.** The extremely high syphilis incidence in one sample of the female homeless population warrants a comprehensive epidemiological, social, and behavioral assessment of the syphilis situation in Nashville's homeless population. It is recommended that such an assessment be conducted, followed by an effective clinical intervention. An innovative approach is needed to provide screening and treatment to this highly mobile population.

4. **Continue to provide quality clinic and laboratory services and health promotion intervention.** With additional syphilis elimination funds from CDC, additional STD services have been added. These services are critical to the control of the syphilis epidemic and should be maintained. Without health promotion, even a successful syphilis control initiative cannot be sustained. It is recommended that an effort be made to improve the combination of educational and environmental supports in our community for healthy behaviors and conditions of living.
5. **Invest in Nashville's public health infrastructure.** According to CDC, the persistence of high rates of syphilis must be viewed as a sentinel public health event. It signals a breakdown in the basic capacity of public health programs to ensure a healthy community (51). The situation of an over-burdened public health system in this community should not be continued. The syphilis epidemic should alert and motivate this community to take prompt corrective action. Therefore, it is recommended that resources be invested in building a strong public health infrastructure in our community. A citizen's task force should be formed to study and strengthen Nashville's public health infrastructure, making Nashville an STD-Free community, and a community in which every citizen can be healthy.

VIII. References

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IX. Appendix

Table A1. Number of Reported P & S Syphilis Cases by Gender and Race, Nashville, TN, 1988-2000

	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	Total	%
Total	83	117	339	290	224	149	100	97	193	203	210	250	200	2455	100.0
Male	46	73	216	151	104	85	51	54	96	106	117	148	117	1364	55.6
Female	37	44	123	139	120	64	49	43	97	97	93	102	83	1091	44.4
White	11	11	53	26	40	21	17	16	14	23	16	32	42	322	13.1
White Male	5	6	36	11	19	13	6	8	10	11	7	13	19	164	6.7
White Female	6	5	17	15	21	8	11	8	4	12	9	19	23	158	6.4
Black	72	106	286	264	183	127	83	79	178	180	193	213	155	2119	86.3
Black Male	41	67	180	140	84	71	45	45	85	95	109	131	95	1188	48.4
Black Female	31	39	106	124	99	56	38	34	93	85	84	82	60	931	37.9
Other*	0	0	0	0	1	1	0	2	1	0	1	5	3	14	0.6
Other Male	0	0	0	0	1	1	0	1	1	0	1	4	3	12	0.5
Other Female	0	0	0	0	0	0	0	1	0	0	0	1	0	2	0.1

Note: *Other is referred to other races rather than black or white.

Figure A1 Reported Cases and Incidence Rates of Primary and Secondary Syphilis, Nashville, TN, 1988-2000

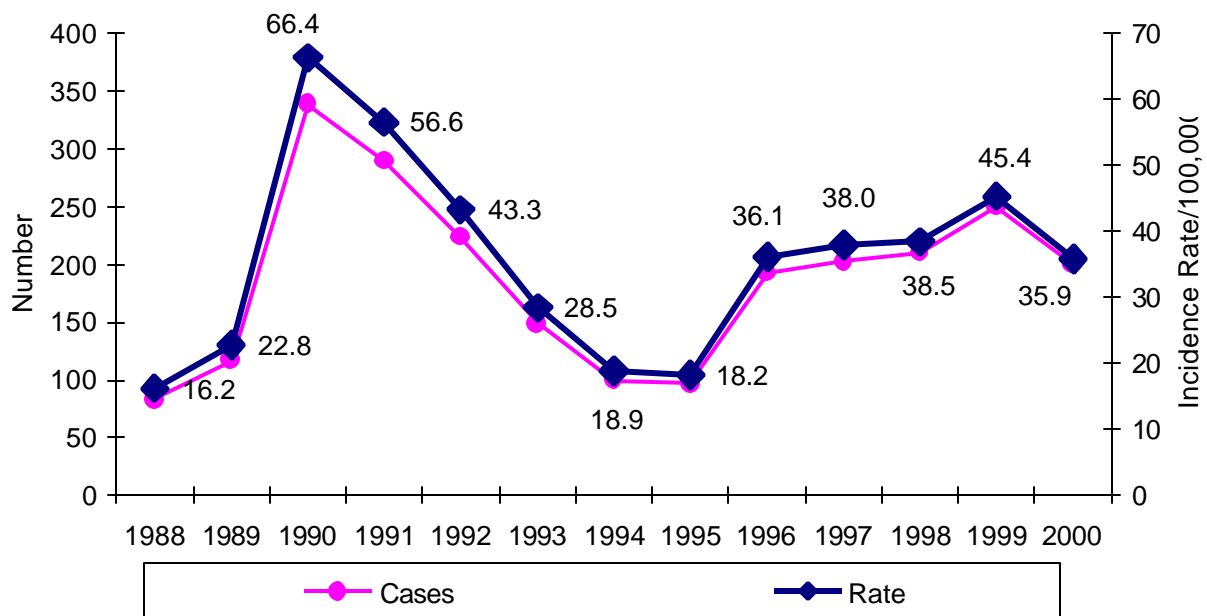


Table A2. Incidence Rates of Reported P & S Syphilis per 100,000 Persons by Gender and Race, Nashville, TN, 1988-2000

	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000
Total	16.2	22.8	66.4	56.6	43.3	28.5	18.9	18.2	36.1	38.0	38.5	45.4	35.9
Male	18.9	30.1	89.1	62.1	42.4	34.3	20.4	21.4	37.9	42.0	45.4	56.8	44.4
Female	13.8	16.4	45.8	51.6	44.1	23.3	17.6	15.3	34.4	34.5	32.4	35.1	28.3
White	2.9	2.9	13.9	6.8	10.4	5.4	4.4	4.1	3.6	5.9	4.0	8.0	10.4
White Male	2.7	3.3	19.7	6.0	10.4	7.0	3.2	4.3	5.3	5.9	3.7	6.8	9.9
White Female	3.0	2.5	8.5	7.5	10.5	4.0	5.4	3.9	2.0	5.9	4.3	9.1	10.9
Black	60.4	88.9	239.8	218.4	148.5	101.0	64.7	60.5	134.4	135.0	140.4	152.0	108.5
Black Male	74.6	121.9	327.6	251.7	148.3	123.0	76.5	75.3	140.3	156.0	173.8	205.0	146.0
Black Female	48.2	60.6	164.8	190.0	148.6	82.3	54.7	48.0	129.4	117.4	112.4	107.5	77.1
Other*	0.0	0.0	0.0	0.0	9.9	9.7	0.0	18.7	9.2	0.0	8.9	43.5	25.6
Other Male	0.0	0.0	0.0	0.0	19.4	19.0	0.0	18.4	18.1	0.0	17.5	68.8	50.7
Other Female	0.0	0.0	0.0	0.0	0.0	0.0	0.0	19.0	0.0	0.0	0.0	17.6	0.0

- Note: 1. 1988-1989 incidence rates were calculated using 1990 census population.
2. 1991-2000 incidence rates were calculated using TDH population projection based on 1990 census population. The data for 1990-1998 were accessed electronically from the TDH STD/HIV program on 9/20/99, the data for 1999 were accessed on 3/8/2000, the data for 2000 were accessed on 6/6/2001.
3. *Other refers to races other than black or white.

Table A3. Number and Incidence Rate per 100,000 of P & S Syphilis by Gender and Age, Nashville, TN, 1998-2000

	1998*						1999**						2000**					
	Male		Female		Total		Male		Female		Total		Male		Female		Total	
	#	Rate	#	Rate	#	Rate	#	Rate	#	Rate	#	Rate	#	Rate	#	Rate	#	Rate
0-14	0	0	0	0	0	0	1	2	1	2	2	2	0	0	0	0	0	0
15-19	6	33	12	68	18	50	4	22	8	45	12	33	7	38	8	45	15	41
20-29	31	74	27	60	58	67	24	58	34	77	58	68	29	70	25	57	54	64
30-39	29	65	31	66	60	66	58	131	43	91	101	110	37	84	35	74	72	79
40-49	34	86	20	46	54	65	47	114	14	31	61	71	30	71	12	26	42	47
50+	17	30	3	4	20	15	14	25	2	2	16	12	14	24	3	4	17	12
All	117	45	93	32	210	39	148	57	102	35	250	45	117	44	83	28	200	36

* The 1998 population used to calculate rates was based on a projection by TDH June 1998 based on 1990 Census, and was accessed electronically on September 20, 1999 through TDH STD/HIV Program.

** The 1999 population used to calculate rates was based on a projection by TDH June 1998, based on 1990 Census and was accessed electronically on March 8, 2000 through TDH STD/HIV Program. The data for 2000 were accessed on 6/6/2001.